Why Are CD8 T Cell Epitopes of Influenza A Virus Conserved?

Z.-R. Tiger Li[1,2], Veronika I. Zarnitsyna[2], Anice C. Lowen[2], Daniel Weissman[1,3], Katia Koelle[1], Jacob E. Kohlmeier[2], Rustom Antia[1]
[1]Department of Biology, [2]Department of Microbiology and Immunology, [3]Department of Physics, Emory University, Atlanta, Georgia.

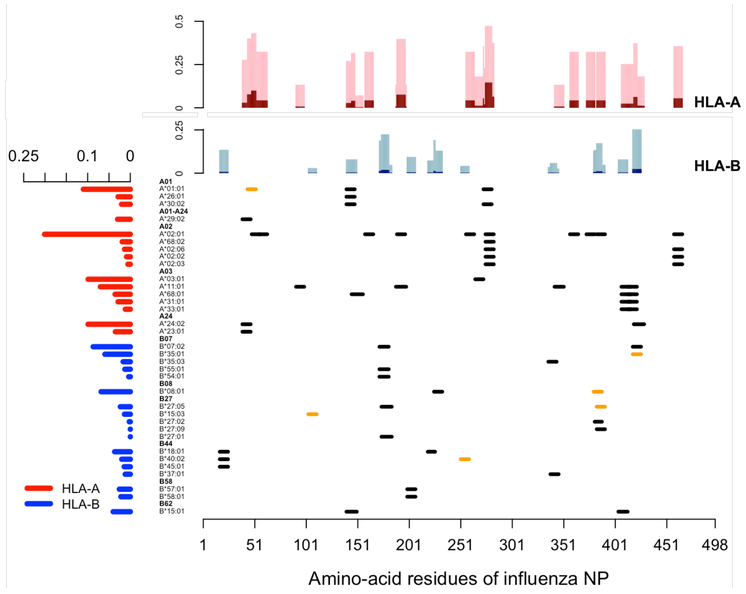
Introduction

Evidences of the conservation

- The internal proteins have lower nonsynonymous mutation rates than the surface proteins.
- Within NP and M1, the CD8 T cell epitope region has less sites of *dN/dS* > 1 than nonepitope region.
- Heterosubtypic infection is cross-protected by pre-existing CD8 T cells in mice and human.

Hypotheses

1. Fitness cost constrains the nonsynonymous mutation.
2. Escape from CD8 T cells brings small selective advantage since CD8 T cells mainly contribute to controlling pathology.
3. MHC polymorphism limits the selective advantage in a fraction of population.



References

Liang et al. *J Immuol* (1994); Bhatt et al. *Mol Biol Evol* (2011);
Sridhar et al. *Nat Med* (2013); Quiñones-Parra et al. *PNAS* (2014);
Mechkovech et al. *J Virol* (2015);
Halloran et al. "Design and Analysis of Vaccine Studies" (2010)

Population Genetics Model

	Host genotypes		
	HH	Hh	hh
Genotype frequency	$(1-f)^2$	$2f(1-f)$	f^2
Relative fitness of WT	1	1	1
Relative fitness of MT	$1-m$	$1-m+Rs$	$1-m+s$

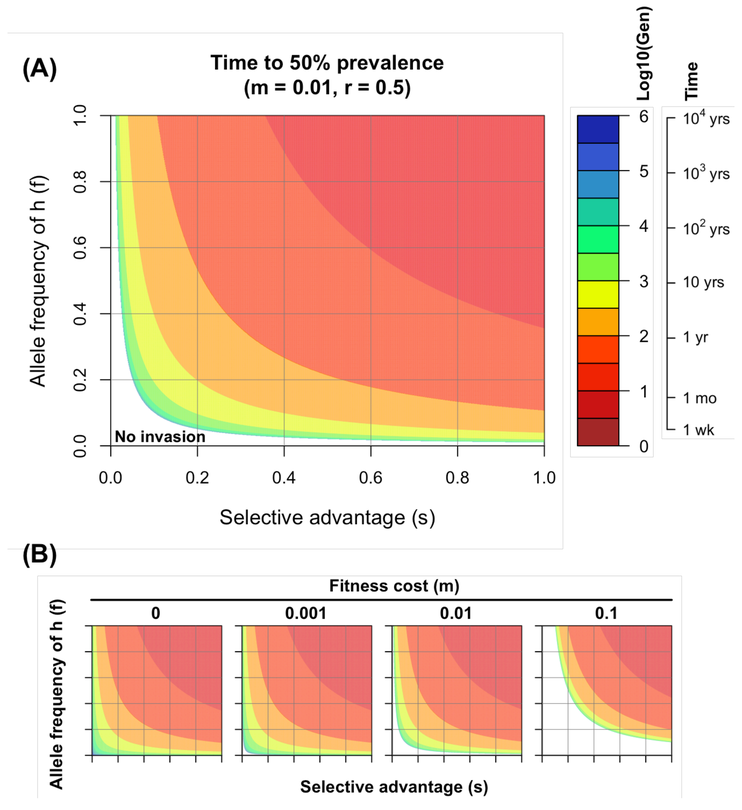
Fitness cost | Heterozygous effect | Selective advantage

$$q_t = \frac{q_{t-1}K}{(1-q_{t-1})+q_{t-1}K} \Rightarrow \frac{q_t}{1-q_t} = K^t\left(\frac{q_0}{1-q_0}\right)$$

q_t: MT prevalence at generation t

K: Mean fitness of MT
$K = (1-f)^2(1-m) + 2f(1-f)(1-m+Rs) + f^2(1-m+s)$

K^t: Growth rate of MT:WT ratio

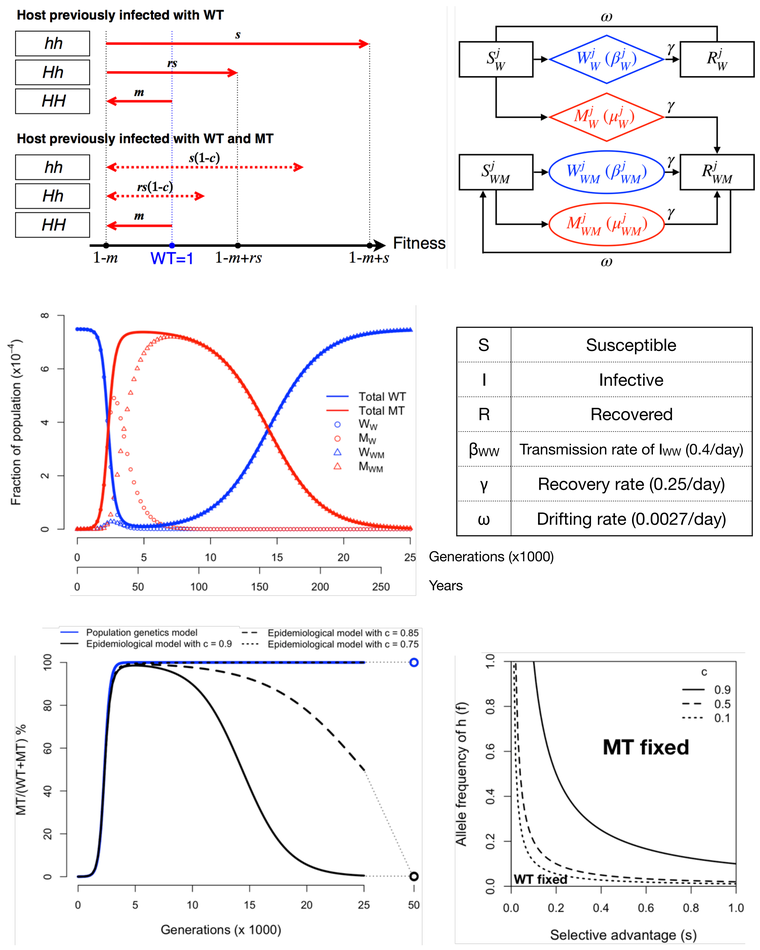


Epidemiological Model

Escaping mechanisms

1. Mutation abrogates peptide-MHC binding.
2. Conformation change prevents TCR recognition.

Compensatory immunity may be induced by the MT infection and decreases the selective advantage.



S	Susceptible
I	Infective
R	Recovered
β_{WW}	Transmission rate of I_{WW} (0.4/day)
γ	Recovery rate (0.25/day)
ω	Drifting rate (0.0027/day)

Conclusion

1. Small selective advantage and MHC polymorphism can account for the low invasion rate of CD8 T cell-escaping mutations, even if fitness cost is absent.
2. Compensatory immunity against mutant may further keep the invasion transient.

If you are interested in this study, please contact **Tiger Li** at **tiger.li@emory.edu**

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